

Exposure-Response Analysis For Pacritinib (SB1518), a Novel Oral JAK2/FLT3 Inhibitor, in Patients with Myelofibrosis

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INTRODUCTION

- Background.** Pacritinib (SB1518) is a novel oral JAK2-FLT3 inhibitor. To date, the pharmacokinetics of once-daily (QD) regimen of pacritinib has been characterized in two studies in healthy volunteers (n=42) and in two phase 1/2 clinical trials in patients with advanced myeloid malignancies (n=129). Due to less-than-proportional increase in systemic exposure with dose, administration of QD doses higher than 400 mg does not appreciably increase systemic exposure of pacritinib. Hence, the twice-daily (BID) regimen was conceived as an alternate dosing regimen to achieve higher systemic pacritinib exposure and potentially enhance clinical response of pacritinib.
- Aims.** Characterize exposure-response relationship of pacritinib using early stage clinical data to support alternate dosing regimens in late stage clinical development.

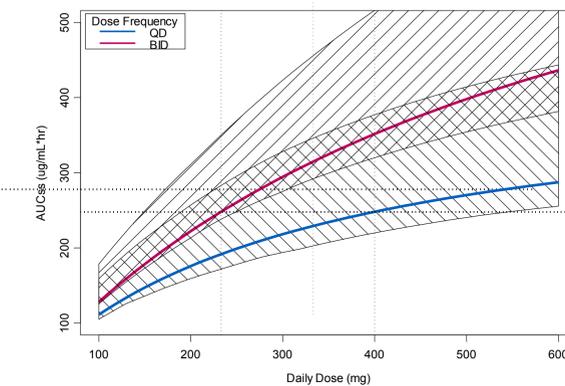
METHODS

- Two pharmacokinetic (PK) studies were conducted in healthy volunteers to assess the inter- and intra-individual PK variability and the effect of food on the PK of pacritinib. Two Phase 1/2 trials were also undertaken to characterize the population pharmacokinetics, safety and efficacy of pacritinib in patients with advanced myeloid malignancies following oral administration of 100-600 mg QD. Safety (i.e., incidence and severity of key AEs including composite gastrointestinal [GI], thrombocytopenia and anemia) and efficacy (i.e., spleen size reduction) of pacritinib were assessed in patients. Based on the safety, tolerability and anti-tumor activity observed in the completed Phase 1 trials, the 400 mg QD regimen of pacritinib was initially selected for further clinical development in MF in Phase 2 trials.
- A total of 65 patients received the 400 mg QD oral pacritinib regimen in Phase 2 trials. To explore the exposure-response relationship following QD dosing of pacritinib, patients with pharmacokinetic exposure data from completed Phase 1/2 trials (n=129) were divided into quartiles (Q1-Q4) based on their exposure as defined by the model predicted area under the curve at steady-state (AUCss). For each exposure quartile, the mean reduction in spleen size was determined. In addition, exposure-response analysis on key safety parameters was similarly performed by comparing AE distributions across exposure quartiles. The key PK parameters were simulated for the 200 mg BID regimen and distribution of patients that fell into QD regimen-defined exposure quartiles was determined.

RESULTS

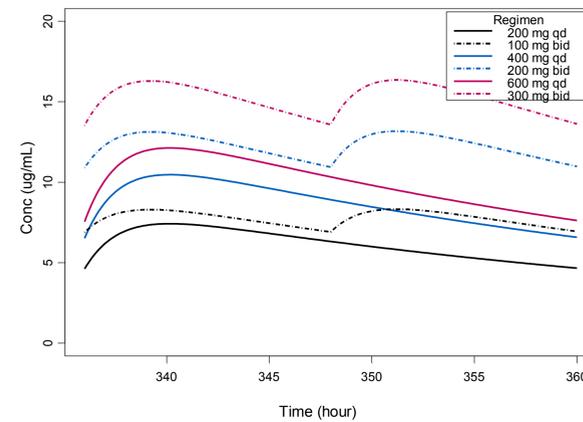
- Efficacy time-course revealed that patients in the highest quartile (Q4) of 400 mg QD pacritinib exhibited the highest maximal response as well as the most durable clinical response over time relative to those that fell in the lower exposure quartiles (Figure 1).
- Based on PK modeling and simulation, the 200 mg BID regimen is predicted to result in a mean systemic exposure that is 41% higher relative to that of the 400 mg QD regimen. We hypothesize that the predicted increase in exposure with 200 mg BID is due to higher drug accumulation and reduced effect of saturable absorption processes on oral bioavailability of pacritinib.
- Approximately 48% of patients on the 200 mg BID regimen are projected to achieve exposures in the highest quartile of exposure achieved by patients that received 400 mg QD in Phase 1/2 trials. In comparison, approximately 25% of patients on 400 mg QD regimen achieved exposure levels in the highest quartile based on Phase 1/2 trial data.
- Incidence and severity of key AEs, such as GI and thrombocytopenia, did not show a clear exposure-safety relationship with pacritinib.

AUCss vs. Dose (mean and 90%CI)



Dashed area represents 90% predictive interval (from model uncertainty and inter-individual variability)

Simulated Conc vs. Time Profile for QD and BID Regimens at Steady-State (Day 15)



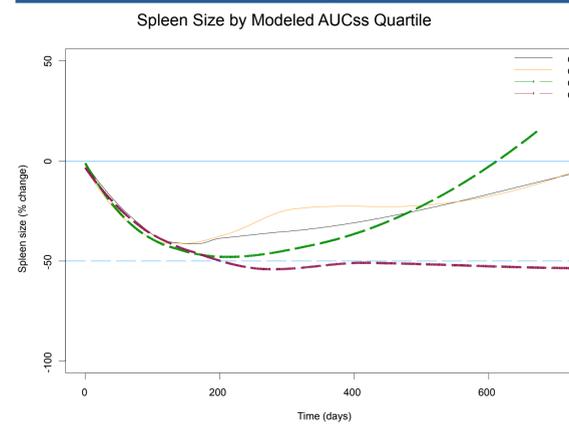
Simulated PK Parameters at Steady-State for QD and BID Regimens

PK Parameters	Dose Frequency	Daily dose (mg)			
		200	400	600	800
AUC _{ss} (µg·hr/mL)	BID	222.2* [213.5–311.2]	351.7 [320–516.2]	436.4 [381.6– 651]	496.2 [421.8–758.8]
	QD	175.8 [159.2–257]	248.1 [220–377.2]	287.5 [255.6–443.5]	312.2 [277.1–486.1]
% of patients within Q4 of 400 mg QD**	BID	19.7	47.8	62.3	69.2
	QD	10.5	25.4	34.1	39.3
C _{max} (µg/mL)	BID	8.3	13.2	16.4	18.6
	QD	7.4	10.5	12.1	13.2

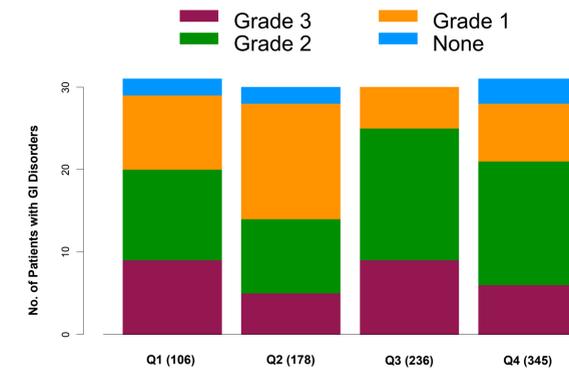
*Predicted [90% predictive interval]

** Q4 (75%tile) of 400mg QD ~ 358 µg·hr/mL. Average of 100 trials with arm size N=1000.

Mean Response by AUC Quartile



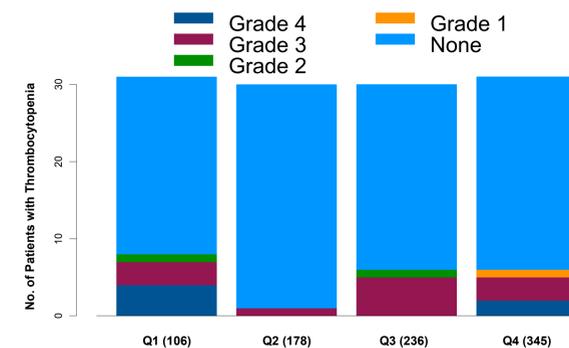
Worst GI Disorder¹ AE by Exposure Quartile



*Patients could have grade 3-4 GI disorder at study entry thus these numbers do not represent treatment-emergent effects.

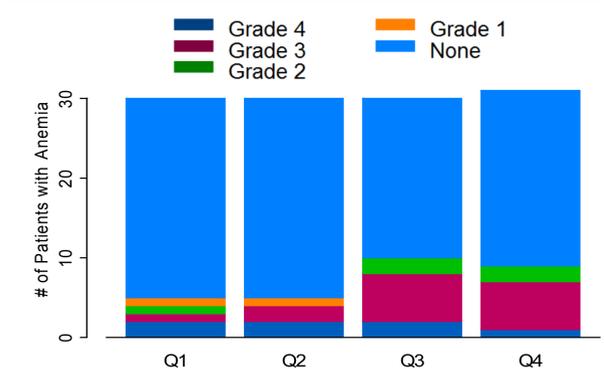
¹GI disorders include diarrhea, nausea, vomiting, constipation and abdominal pain.

Worst Thrombocytopenia AE by Exposure Quartile



*Patients could have grade 3-4 thrombocytopenia at study entry thus these numbers do not represent treatment-emergent effects.

Worst Anemia AE by Exposure Quartile



*Patients could have grade 3-4 anemia at study entry thus these numbers do not represent treatment-emergent effects.

CONCLUSIONS

- The exposure-safety and exposure-efficacy analyses support the potential utility of the 200 mg BID regimen of pacritinib in addition to the 400 mg QD regimen for the clinical development of pacritinib for myelofibrosis, as well as other indications such as FLT3-mutated AML.
- The higher proportion of patients expected to achieve the Q4 exposure levels with the 200 mg BID regimen is predicted to result in higher splenic response rates compared to the 400 mg QD regimen.
- There was no clear exposure-response relationship on key AEs including GI, anemia and thrombocytopenia AEs. The lower local concentration of pacritinib in the GI tract with BID regimen may potentially decrease the incidence of GI adverse events such as diarrhea.